

## Cartridge for a liquid

10 The invention concerns a cartridge for a liquid, which can be connected to a draw-off or dispensing device. The dispensing device includes an upper portion which accommodates the cartridge and a lower portion which can be pushed on over the connected cartridge. The upper portion of the device is provided with a connecting portion for the cartridge and with a dispensing connection portion for drawing off and  
15 dispensing the liquid.

Liquids in accordance with the present invention can be solutions, suspensions or emulsions. Preferred liquids are those which contain an active substance. Active substances can be pharmacologically active substances for treatment of the human or animal body or active  
20 substances for diagnostic purposes or for a cosmetic use.

The invention aims to adapt an economically manufacturable cartridge of that kind to specific demands.

Different thin-wall containers of the general kind set forth, for a liquid, are known, which are not diffusion-tight in relation to volatile  
25 constituents of the liquid. In that case a part of the liquid is lost by diffusion and the level of concentration of constituents of the liquid changes in a manner which is possibly unacceptable. Containers of that kind are suitable for a relatively short storage time. In the case of other containers of the general kind set forth, unacceptable changes in the liquid  
30 occur due to diffusion or due to the action of air, prior to or during the period of use. Particularly in the case of containers for a liquid which contains medical active substances, there is a need to satisfy intensified

demands in order to avoid unacceptable adverse effects on the quality of the medicament.

Accordingly the object of the invention is to develop a cartridge for a liquid, which can be economically produced even in large numbers and which in the filled condition can be stored over a long period of time even under difficult conditions. The invention seeks to provide that the liquid can be easily drawn off and not involve contact with the environment. The invention further seeks to provide that the cartridge can be connected to a draw-off or dispensing device as easily as possible and interchangeably and that the cartridge can be reliably handled even by unskilled persons. The invention further seeks to provide that the cartridge is also suitable for a liquid which contains medical active substances and satisfies the intensified conditions which occur in that situation.

In accordance with the invention that object is attained by a cartridge which can be connected to a draw-off or dispensing device. The dispensing device includes an upper portion which accommodates the cartridge and a lower portion which can be pushed on over the connected cartridge. The upper portion of the device is provided with a connection portion for the cartridge and with a draw-off or dispensing connection portion for drawing off the liquid. The cartridge can be in the form of a triple-shell container comprising an outer stiff casing, a container which is stable in respect of shape and which is disposed in the casing, and a collapsible bag which is arranged in the container that is stable in respect of shape and which contains the liquid. The stiff casing can have a bottom which can be provided with an opening. The container which is stable in respect of shape can also have an opening and can be closed with a stopper provided with an insertion connection portion. The stopper can form a sealingly closing, centred guide means for the draw-off connection portion. The stopper can be non-releasably connected by the stiff casing to the container which is stable in respect of shape. The cartridge can be

releasably connected to the connection portion at the upper portion of the dispensing device.

The connection between the cartridge and the connection portion of the device can be in the form of a plug-in connection, a screw connection  
5 or a bayonet connection. This connection can preferably be a releasable connection. Optionally, it can be in the form of a non-releasable connection or a connection which is difficult to release.

The stopper can preferably comprise a thermoplastic material and can be connected to the container that is stable in respect of shape, in  
10 force-locking and positively locking relationship, by means of a snap-action connection. The stopper can also be non-releasably welded to the container that is stable in respect of shape and that comprises thermoplastic material, by the materials merging together. The stopper can be provided in the insertion connection portion with a funnel-shaped  
15 centred guide means for the dispensing or draw-off connection portion. The guide means can be provided with guide ribs. The stopper can sealingly embrace the draw-off connection portion and can be in the form of a press fit for the latter. It may be desirable for the end of the insertion connection portion, that is towards the internal space of the collapsible  
20 bag, to be closed by a diaphragm which can be arranged inclinedly relative to the axis of the insertion connection portion and which can be pierced when the draw-off connection portion is introduced into the cartridge. That diaphragm prevents the liquid from escaping into the insertion connection portion during storage of the cartridge.

25 A sealing disc which can be provided with sealing beads or ridges can be provided between the upper edge of the container which is stable in respect of shape, and the inside of the stopper. The inside of the stopper can be provided with a sealing lip or a plurality of sealing lips which are pressed into the sealing disc on the upper edge of the container  
30 which is stable in respect of shape.

Apart from its opening, the stiff casing is diffusion-tight in relation to gases and liquids. This casing can be a one-piece deep-drawn metal casing, preferably of aluminium. The stiff casing can also be of a two-piece construction; then, the two parts of the casing are joined together and sealed off relative to each other by way of sealing elements by welding or by adhesive. The stiff casing can also comprise a plastic material, preferably a thermoplastic material.

The stiff casing can have a projecting bead or ridge at the edge of its bottom. The bottom can be provided with a recess which is arranged centrally as an inwardly turned region of the bottom.

The stiff casing preferably has at the centre point of the bottom an opening which can be in the form of a bore. It is additionally possible to provide in the recess in the bottom of the casing an insert which preferably comprises plastic material and which includes an opening in the form of a micro-opening which communicates with the opening in the bottom of the stiff casing. A filter can be disposed in front of the micro-opening within the insert.

The opening in the bottom of the stiff casing can be of a diameter of between 0.1 mm and 5 mm when the cross-section involved is circular. The micro-opening in the insert, when a circular cross-section is involved, is between 10  $\mu\text{m}$  and 500  $\mu\text{m}$  in diameter and between 100  $\mu\text{m}$  and 5000  $\mu\text{m}$  in length. The micro-opening makes it possible to adjust to a desired value the time for pressure equalisation between the internal space in the cartridge and its environment.

The stiff casing of metal can be provided in the proximity of its open end with a peripherally extending crease which embraces the stopper in force-locking and positively locking relationship. The stiff casing of thermoplastic material can be welded to the stopper, with merging of the materials thereof. In addition in its upper part the stiff casing can be provided with a peripherally extending, outwardly open groove which extends around the lower edge of the stopper. At its open end the stiff

The stiff casing can be provided with a plurality of projections which protrude into the interior of the casing and which support the container which is stable in respect of shape within the stiff casing. Preferably three projections are disposed in the middle to the lower region of the stiff casing, which are disposed in a plane which is perpendicular to the axis of the casing. In the case of a stiff casing of metal, those projections can be produced when flanging the open end of the stiff casing.

The releasable connection between the cartridge and the connection portion of the dispensing device can be a plug-type connection in which the connection portion is provided with a plurality of snap hooks which engage into the peripherally extending groove in the upper part of the stiff casing after the cartridge has been inserted into the device. The plug connection can advantageously also be used for other containers of the general kind set forth, in which case the container which is stable in respect of shape or the stopper includes a groove into which the snap hooks engage.

Snap hooks of plastic material can be provided with a metal spring element which maintains the spring property of the snap hooks over a long period of time and at elevated temperature.

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A free space which is covered by the sealing foil can be provided in the central region of the sealing foil on the outside of the bottom of the casing. A rigid or resilient piercing device can be disposed on the inside of the bottom of the lower portion of the device, the piercing device piercing the sealing foil disposed on the underside of the bottom of the casing, prior to the first withdrawal of a part of the liquid from the cartridge. That opens the opening in the bottom of the casing or the micro-opening in the insert and permits air to pass into the space inside the cartridge.

To remove a used cartridge from the dispensing device, it is possible to use a withdrawal aid which is pushed under the bead or ridge at the bottom of the stiff casing, thereby to make it easier to pull the cartridge out.

Before the cartridge is connected to the dispensing device, the sealing foils on the stopper and on the bottom of the cartridge are detached or those sealing foils are pierced when the cartridge is connected to the dispensing device. A difference in pressure which possibly prevails between the interior of the cartridge and the environment around the cartridge is equalised through the opening in the bottom of the stiff casing.

When a quantity of liquid is drawn out of the cartridge connected to the dispensing device, the collapsible bag collapses and its volume is reduced by the volume of the quantity of liquid which is drawn off. As a result there is a reduced pressure in the gas space of the cartridge (this is the free space between the outside of the collapsible bag and the inside of the stiff casing) in comparison with the pressure in the ambient atmosphere around the cartridge. That pressure difference is equalised in a relatively short period of time if the stiff casing is thin-walled and is provided with a bore in the region of between 0.1 mm and 5 mm.

If the cartridge is provided in the bottom of the stiff casing with an insert which includes a micro-opening, it is possible to adjust the time for pressure equalisation between the gas space in the cartridge and the

ambient atmosphere. For example with a volume of 3 millilitres of the gas space in the cartridge and a pressure difference of 20 hPa (20 mbar) between the ambient atmosphere around the cartridge and the gas space in the cartridge, in the case of a circular micro-opening of a length of 200  
5  $\mu\text{m}$  and a diameter of between 80  $\mu\text{m}$  and 50  $\mu\text{m}$ , it is possible to achieve a half-value time for pressure equalisation of between 2 hours and 13 hours.

In the case of a pressure equalisation time which is adapted to the usual time interval between two operations of drawing off liquid from the  
10 cartridge, the diffusion of constituents of the liquid out of the collapsed bag is made more difficult.

The cartridge according to the invention can be for example 55 mm in length and 17 mm in diameter. The stopper can have an insertion connection portion whose inside diameter gives a firm press fit on a  
15 dispensing connection portion of an outside diameter of 2 mm.

The cartridge according to the invention can be used in an atomiser as is shown in Figures 6a and 6b in WO - 97/12687. The cartridge (1) of the present invention corresponds to the supply container (71) in Figures 6a and 6b, the spring portion of the locking clamping mechanism, in the  
20 form of connection portion (2), corresponds to the spring portion (56), and the lower portion (3) of the device corresponds to the lower housing portion (70).

The cartridge may contain an aqueous or alcoholic liquid.

When an aqueous liquid is involved, the container which is stable in  
25 respect of shape and the stopper can comprise polypropylene. The collapsible bag can comprise polyethylene. The stiff casing can comprise plastic material, preferably polypropylene. The opening in the bottom of the stiff casing can be a bore. The stopper for the container which is stable in respect of shape can be provided with an insertion connection  
30 portion which, at its end towards the internal space, can be closed with a diaphragm which is inclined relative to the axis of the insertion connection

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portion. The insertion connection portion can involve a press fit for the dispensing connection portion. The stopper can be connected to the container which is stable in respect of shape by a snap connection. The releasable plug-in connection between the cartridge and the connection  
5 portion of the dispensing device can be a snap connection in which the snap hooks in the connection portion of the dispensing device engage into the peripherally extending groove in the upper region of the cartridge. the inside of the bottom of the lower portion of the device which is fitted on the upper portion can be provided with a resilient piercing device for the  
10 sealing foil on the underside of the bottom of the casing.

In the case of an alcoholic liquid the container which is stable in respect of shape and the stopper can comprise polypropylene. The collapsible bag can comprise polyethylene. The stiff casing can comprise metal, preferably aluminium. The recess in the bottom of the stiff casing  
15 may receive an insert with a micro-opening which communicates with the bore in the bottom of the casing. The stopper provided with an insertion connection portion, for the container which is stable in respect of shape, can be closed at its end towards the internal space by a diaphragm which is inclined with respect to the axis of the insertion connection portion. The  
20 insertion connection portion can be provided with a sealing closing centred guide means for the dispensing connection portion, the guide means being in the form of a press fit. The stopper can be non-releasably connected to the container which is stable in respect of shape, by means of the stiff casing. The releasable plug connection between the cartridge and the  
25 connection portion of the dispensing device can be a snap connection in which the snap hooks in the connection portion of the dispensing device engage into the peripherally extending groove in the upper region of the cartridge. The inside of the bottom of the fitted-on lower portion of the device can be provided with a resilient piercing device for the sealing foil  
30 on the underside of the bottom of the casing.

The cartridge according to the invention can be filled with a medical liquid which for example contains a pharmacologically active substance and for example water, ethanol or mixtures thereof.

WO - 98/27959 describes stabilised aqueous medicament  
5 preparations for producing propellant gas-free aerosols for inhalation.  
Attention is directed to the formulations which are claimed therein and set  
forth in the Examples.

Suitable medicament preparations in an ethanol solution are set forth for example in WO - 97/01329, and in particular attention is directed to the active substances referred to therein (see therein pages 2 and 3) and the stabilised formulations claimed therein.

As medical active substances it is possible to use Berotec (Fenoterol hydrobromide); 1-(3,5-dihydroxy-phenyl)-2-[[1-(4-hydroxy-benzyl)-ethyl]-amino]-ethanol hydrobromide), Atrovent (Ipratropium bromide), Berodual (combination of Fenoterol hydrobromide and Ipratropium bromide), Salbutamol, Salbutamol sulphate, Combivent, Oxivent (Oxitropium bromide), Ba 679 (Tiotropium bromide), BEA 2108 (di-(2-thienyl)-glycolic acid tropenol ester), Flunisolid, Budesonid, Beclomethasone and others.

20           The cartridge according to the invention enjoys the following advantages:

- The concentration of the medical liquid contained in the sealed cartridge varies only to a tolerable extent even over a storage time of several years and at elevated storage temperature.
- 25        - The content of the cartridge is highly effectively protected from contamination.
- The cartridge when fitted into the dispensing device can be used over several months.
- The half-value time for pressure equalisation can be adjusted
- 30        by the shape of the micro-opening.
- The cartridge can be produced in medically acceptable form.

- The unmodified original condition of the cartridge and the content thereof can be readily perceived within the specified period of usability by virtue of the intact sealing foils.

- The cartridge has a high degree of functional reliability;  
5 mishandling is avoided.

- The cartridge is securely held in the dispensing device.

- The fixedly closed cartridge is child-proof and makes it more difficult to manipulate the content thereof.

- The empty cartridge can be easily pulled out of the  
10 dispensing device because of the ridge at the bottom of the stiff casing.

The cartridge according to the invention which contains a medical liquid can be used to produce an inhalable aerosol by means of an atomiser. The aerosol can serve for treating illnesses.

The cartridge according to the invention is described in greater  
15 detail by means of the drawings.

Figure 1 shows the cartridge 1, the connection portion 2 of the draw-off or dispensing device and the lower portion 3 of the device which is pushed over the connected cartridge. The stiff casing 4 contains the container 5 which is stable in respect of shape, with the collapsible bag 6.  
20 The container which is stable in respect of shape is closed by the stopper 7 and the snap connection 8. Disposed between the upper edge of the container which is stable in respect of shape and the underside of the stopper is the sealing disc 9 into which the sealing lip 10 is pressed. The stiff casing includes the peripherally extending groove 11 against which  
25 the lower edge of the stopper bears. The peripherally extending crease 12 in the stiff casing is pressed into the stopper. The stopper is held at its top side by the flanged-over portion 13 of the upper end of the stiff casing. The opening 14 is provided in the container 5 which is stable in respect of shape.

30 The connection portion of the dispensing device includes the dispensing or draw-off connection portion 15 which has already pierced

the sealing foil 16 on the top side of the stopper and which has penetrated into the insertion connection portion 17. When the cartridge is further pushed onto the dispensing connection portion 15 it penetrates the region 17a of the press fit and pierces the inclined diaphragm 18 at the end of the insertion connection portion 17. The snap hooks 19 on the connection portion 2 of the dispensing device engage from the outside into the peripherally extending groove 11 in the stiff casing.

The stiff casing 4 is provided in its central region with projections 4a which are disposed in a plane which is perpendicular to the axis of the casing. Those projections support the container which is stable in respect of shape.

The stiff casing is provided at its bottom edge with the projecting ridge or bead 20. Disposed in the centre of the recess in the form of the inwardly inverted region 21 is the opening 22 in the stiff casing. The bottom of the stiff casing is covered by the sealing foil 23. The free space 24 is to be found between the sealing foil and the inwardly curved region. The resilient piercing device 25 is disposed on the inside of the lower portion 3 of the dispensing device.

Figure 2 shows the cartridge 1 when it has been completely pushed onto the dispensing connection portion and connected to the connection portion 2. The diaphragm at the end of the insertion connection portion is pierced and the snap hooks 19 engage into the peripherally extending groove at the upper end of the stiff casing. The stopper 7 is provided with guide ribs 7a. The region 17a involves a press fit between the dispensing connection portion and the stopper. The insert 26 is disposed in the recess in the form of the inwardly inverted region of the bottom of the casing.

Figure 3a shows the end of the stiff casing 4, the end of the lower portion of the dispensing device and the insert 26 on an enlarged scale. The insert 26 includes the micro-opening 27 which communicates with the opening 28 in the bottom of the stiff casing. Disposed in front of the

micro-opening is the filter 29. The bottom of the stiff casing is covered by the sealing foil 23.

Figure 3b shows the condition in which the piercing device 25 has pierced the sealing foil 23.

5        Figure 4a shows a cross-section through the withdrawal aid 30 which is fitted onto the cartridge 1 and which has pressed the stiff casing in, behind the ridge or bead 20. The cartridge is clamped in position in the withdrawal aid 30 and can be turned about the axis of the cartridge and pulled out of the dispensing device by means of the withdrawal aid.

10        Figure 4b shows a view from above of the withdrawal aid 30 in the condition of being fitted on the cartridge and the stiff casing 4 in cross-section. The withdrawal aid 30 includes an opening with a centrally arranged region whose diameter is substantially the same as the outside diameter of the stiff casing 4 and which is smaller than the diameter of the  
15        bead or ridge 20. The central region of the opening goes into an enlarged opening 31 so that the withdrawal aid can be easily fitted onto the end of the cartridge. The diameter of the central region of the opening is reduced at two mutually diametrically oppositely disposed locations 32 and 33 and the circular arc of the opening is flattened. At those locations, the  
20        stiff casing of the cartridge is compressed when the withdrawal aid is pushed on, whereby a tight connection is made between the withdrawal aid and the cartridge.